

REMARKS

Claims 1-5 are pending. Claims 1-3 are amended. Support for the amendment may be found throughout the application as originally filed; for example, pages 15, 16, and 18. No new matter is added.

Claim Rejections under 35 USC §103:

Claims 1-5 are rejected under 35 USC §103(a) as alleged being unpatentable over WO93/04077 ('077 document). Specifically, the examiner states that *"The '077 document is drawn to various enzyme substrates overlapping in structure with those instantly claimed. See claim 7 for example, where W is N-R and R is an alkyl group containing 4 carbon atoms...It is noted in claim 7 of the '077 document there are only 6 different moieties for W and also few choices for lower alkyl groups which have between 1 and 4 carbon atoms. As such, there is seen to be a finite number of identified, predictable solution wherein the skilled artisan would have a reasonable expectation of success"*. Applicants respectfully traverse.

The '077 document discloses substrates which are non-fluorescent and react with enzymes to generate fluorescent phenolic precipitates; see page 9, first paragraph. The '077 document does not provide any reason to modify the substrate in any way for the intended purpose of the present invention as described below.

The present application is directed to novel fluorogenic hydrolase substrates having increased permeability for cell membranes without affecting photostability. The improved properties are due to the substitution of a lipophilic group on the fluorophore moiety with an apolar side-chain (i.e. at least one of R1, R2 or R3 groups having at least 4 carbons). Such substitution results in a larger molecule which generally has poor permeability for cell membranes. Contrary to the conventional wisdom, applicants discovered that the compounds of the present invention can easily enter cytoplasm without any additional chemical, such as DMSO, or physical, such as electroporation, treatments. Therefore, the claimed compounds may be used to measure hydrolase activity without disrupting cell membranes, such as a cell-based assay. See page 5, lines 33-38; page 6, lines 1-3; page 19, line 5-10; and page 41, Example 7.

MPEP states that predictability and reasonable expectation of success should be determined at the time the invention was made. See MPEP 2143.02, *"Whether an art is predictable or whether the proposed modification or combination of the prior art has a*

reasonable expectation of success is determined at the time the invention was made. Ex parte Erlich, 3 USPQ2d 1011 (Bd. Pat. App. & Inter. 1986)". The "permeability" property of the claimed compounds was discovered by applicants. There is no teaching or suggestion in the '077 document about such properties. Nor is there any motivation for one skilled in the art to modify the compound in the way disclosed therein. Absent such teaching, suggestion or motivation, one skilled in the art at the time of the present invention was made would have no reason to modify the substrate of the '077 document to produce the claimed compounds.

Accordingly, the rejection under 35 USC §103(a) has been overcome and should be withdrawn.

Claim Rejections under 35 USC §112:

Claims 1-5 are rejected under 35 USC §112, second paragraph, as alleged being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, claim 1 is rejected for reciting the terms "R₁" and "R₄O-"; claims 1 and 2 are rejected for lacking the alternative term "or" and the definition of the terms "Het¹" and "Het²", and for reciting the term "derivative".

In response, Applicants amend claims 1 and 2 as suggested by the examiner. Briefly, claim 1 is amended to recite "R₁" and "R₄O-" and claims 1 and 2 are amended to incorporate the alternative term "or" and the definitions of the terms "BLOCKING GROUP", "Het¹" and "Het²".

Accordingly, the rejection is obviated. Reconsideration and withdrawal of the rejection under 35 USC §112 are respectfully requested.

Applicants respectfully request that a timely Notice of Allowance be issued in the present application.

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